Monocyte/High-Density Lipoprotein Ratio as an Inflammatory Marker in Patients with Irritable Bowel Syndrome

Çağdaş Erdoğan1,*, Ibrahim Ethem Güven1, Batuhan Başpınar1, Zeki Mesut Yalın Kılıç1

1 Department of Gastroenterology, Ankara City Hospital, Ankara, TR
* Corresponding Author: Çağdaş Erdoğan E-mail: cagdas_edogan@hotmail.com

ABSTRACT

Objective: Irritable bowel syndrome (IBS) is a chronic, functional disorder of the gastrointestinal tract. Recent investigations have highlighted the potential involvement of inflammation, although the etiology of IBS remains unknown. This study aims to assess the connection between IBS and Monocyte/High-Density Lipoprotein (HDL) ratio (MHR), a new inflammatory marker.

Material and Method: The study was conducted in the outpatient gastroenterology unit of a tertiary center between March 2021 and March 2022. Patients with IBS, according to the Rome IV criteria were examined retrospectively. Age- and sex-matched healthy controls were used to compute MHR and compare the results.

Results: A total of 255 participants, 155 diagnosed with IBS and 100 in the control group, were included. The median (min-max) monocyte counts (cells/mm³) in the IBS and control groups were 380.0 (310.0-460.0) and 332.0 (232.0-449.3), respectively (p = 0.008). The median (min-max) HDL levels (mg/dl) in IBS and control groups were 45.0 (36.0-55.0) and 49.0 (43.0-57.0), respectively (p = 0.001). The median MHR was higher in the IBS group (9.5) compared to healthy controls (6.73, p<0.001). Logistic regression analysis revealed MHR as an independent predictor of the presence of IBS (OR: 1.406, 95% CI: [insert confidence interval]). The cut-off value for MHR to detect IBS with 62.6% sensitivity and 63.0% specificity was 7.57, and ROC analysis revealed an AUROC value of 0.646 (95% CI: 0.577-0.715, p<0.001).

Discussion: The study's primary findings were that IBS patients had significantly lower levels of HDL cholesterol and significantly higher levels of monocyte counts when compared to the control group. Consequently, monocyte/HDL ratios (MHR) were statistically substantially greater in IBS patients than in the control group. Furthermore, when the cut-off value was set at 7.6, MHR was found to be an independent predictor for IBS, with 62.6% sensitivity and 63.0% specificity.

Conclusion: MHR can be a simple, inexpensive, and effective tool to demonstrate the inflammatory state in patients with IBS.

Keywords: MHR, Irritable bowel syndrome, inflammation, monocyte/high-density lipoprotein ratio, inflammatory marker

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a chronic and functional disorder of the gastrointestinal (GI) tract, characterized by persistent abdominal pain without any discernible organic pathology and accompanied by altered bowel movements (1). It is characterized by its chronic nature, often leading to substantial impairment in the quality of life of affected individuals. The pathogenesis of IBS has long been a subject of intense research and debate within the medical community. While the diagnostic criteria, such as the Rome IV criteria, have provided a standardized framework for identifying and categorizing IBS (2-4), the underlying mechanisms responsible for its development and persistence continue to elude full comprehension (5).

In recent years, emerging evidence has suggested that inflammation may play a pivotal role in the pathophysiology of IBS (6, 7).
This intriguing hypothesis has been supported not only by histopathological findings demonstrating mucosal inflammation within the gastrointestinal tract (8-11) but also by a range of biochemical markers that point towards an inflammatory underpinning of the disorder. These markers include, among others, the neutrophil-to-lymphocyte count ratio (12), mean platelet volume (13), and red cell distribution width (14), as well as ratios such as MPV to platelet and RDW to platelet ratio (15), all of which have demonstrated associations with IBS.

Of particular interest is the Monocyte-to-HDL Ratio (MHR), a marker grounded in the interplay between monocytes - a crucial component of the innate immune system - and high-density lipoprotein (HDL), which possesses anti-inflammatory and antioxidative properties. Monocytes and macrophages are notable for their capacity to release proinflammatory and prooxidant molecules, while HDL molecules exhibit the ability to counteract these harmful effects. Recognizing this dynamic, the MHR has been proposed as a potentially informative inflammatory marker and has been employed in evaluating various disease states (16-20).

This study aims to contribute to the expanding body of knowledge on IBS by exploring the relationship between the Monocyte-to-HDL Ratio (MHR) and the presence of IBS. The investigation of MHR as an inflammatory marker in the context of IBS may provide valuable insights into the underlying inflammatory processes and offer potential avenues for the development of novel diagnostic or therapeutic approaches for this complex and often debilitating disorder. In doing so, it aims to shed light on the complex pathophysiological landscape of IBS and improve our understanding of this enigmatic condition.

**MATERIAL and METHODS**

**Study Design**

This investigation was carried out within the confines of a solitary tertiary medical center and was structured as a retrospective comparative cohort study. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Approval for the study was obtained from the Ankara City Hospital Scientific Research Assessment and Ethics Committee, bearing the reference number Ethical Board – E1-21-2050. Given the study's retrospective nature, informed consent from participants was not sought.

**Study Population**

The study cohort consisted of patients who sought medical evaluation at the gastroenterology outpatient clinic and were diagnosed with irritable bowel syndrome (IBS) in accordance with the Rome IV criteria during the period spanning from March 2021 to March 2022. Importantly, all enrolled patients had previously undergone total colonoscopy examinations characterized by satisfactory bowel preparation, as denoted by a Boston Bowel Preparation Score of 3. These colonoscopies effectively excluded the presence of organic pathologies within the gastrointestinal tract.

For statistical comparisons, a control group comprising individuals matched for age and sex was assembled. These control participants were recruited from individuals attending the outpatient unit for routine health check-ups, with an additional requirement being the absence of comorbidities or regular medication use.

**Exclusion Criteria**

Exclusion criteria were applied uniformly to both the study and control groups. These criteria encompassed the following: Age under 18 years, presence of any infectious disease, rheumatological disease, autoimmune disease, inflammatory bowel disease, celiac disease, malignancy, diabetes mellitus, hypo or hyperthyroidism, and previous major abdominal surgery. Several disorders have been found to have an impact on MHR when the literature is evaluated. For this reason, participants with previously investigated neurological, psychological, or cardiovascular diseases that may impact MHR were excluded from the study.

**Data Collection**

Comprehensive demographic information for each patient, encompassing age, gender, and smoking status, was meticulously extracted from both digital and printed medical records. Routine outpatient serum biochemical analyses were meticulously scrutinized as part of the data collection process. Specifically, monocyte counts, and high-density lipoprotein (HDL) levels were recorded for each patient, facilitating the subsequent calculation of the Monocyte-to-HDL Ratio (MHR). Additional parameters concerning renal and hepatic function were also systematically documented for all participants.

**Statistical Analysis**

The SPSS 25.0 Statistical Package Program for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables were tested for normality distribution by using Kolmogorov–Smirnov test. Normally scattered continuous variables were stated as mean and standard deviation. Median and quartile deviation (QD) were preferred otherwise. Categorical variables are presented as percentages. Pearson’s chi-square or Fisher’s exact test was performed for percentage comparisons. An independent sample t-test was performed for parametric data, while Mann–Whitney U test was used for nonparametric data. Logistic regression analysis examined the association between IBS and other variables. Variables with p< 0.25 in univariate logistic regression were included in a multiple logistic regression model. Receiver–operating characteristics (ROC) curve analysis was used to predict the presence of IBS. A two-sided p<0.05 was considered statistically significant for all analyses.

**RESULTS**

A total of 255 participants were enrolled in the study. Of the participants, 155 were diagnosed with IBS with a median (QD) age of 47.0 (32.0-57.0) years, and 61 (39.0%) patients were male. The control group had 100 participants with a median age of 45.0 (36.0-55.8) years, and 45 (45.0%) were male. The baseline characteristics and laboratory findings of the study population are presented in Table I. The median (QD) monocyte counts in IBS and control groups were 380.0 (310.0-460.0) and 332.0 (232.0-449.3), respectively (p=0.008).

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The median (QD) HDL-cholesterol levels in IBS and control groups were 45.0 (36.0-55.0) and 49.0 (43.00-57.00), respectively (p=0.001). The median (QD) MHR values were 9.5 (6.1-12.1) in the IBS group and 6.7 (4.7-9.5) in the control group. This difference was statistically significant with a p-value of <0.001.

Univariate and multivariate logistic regression analyses were performed to determine the independent predictors of the presence of IBS. MHR was the independent predictor of the presence of IBS with an OR of 1.4 (CI: 1.1– 1.8, p=0.013) (Table II). The cut-off value of MHR for IBS was 7.6, with a sensitivity of 62.6% and specificity of 63.0%, along with an AUC value of 0.646 (95% CI: 0.577-0.715; p<0.001) on ROC curve analysis (Figure 1).

Table I: Baseline clinical and laboratory parameters of study population.

<table>
<thead>
<tr>
<th></th>
<th>IBS (n=155)</th>
<th>Control (n=100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.0 (32.0-57.0)</td>
<td>45.0 (36.0-55.8)</td>
<td>0.721</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>61 (39.0)</td>
<td>45 (45.0)</td>
<td>0.372</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>45 (29.0)</td>
<td>37 (37.0)</td>
<td>0.184</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl), median (QD)</td>
<td>87.0 (82.0-95.0)</td>
<td>86.0 (81.0-92.8)</td>
<td>0.266</td>
</tr>
<tr>
<td>BUN (mg/dl), median (QD)</td>
<td>28.0 (23.0-34.0)</td>
<td>29.0 (24.3-34.0)</td>
<td>0.426</td>
</tr>
<tr>
<td>Creatinine (mg/dl), median (QD)</td>
<td>0.79 (0.68-0.87)</td>
<td>0.76 (0.65-0.82)</td>
<td>0.069</td>
</tr>
<tr>
<td>Hemoglobin (g/dl), median (QD)</td>
<td>13.7 (12.9-15.3)</td>
<td>14.0 (13.1-14.8)</td>
<td>0.791</td>
</tr>
<tr>
<td>Platelet count (x10³/mm³), median (QD)</td>
<td>246.0 (205.0-302.0)</td>
<td>239.0 (197.3-280.8)</td>
<td>0.083</td>
</tr>
<tr>
<td>WBC count (x10³), mean ± SD</td>
<td>7.1 ± 1.6</td>
<td>6.9 ± 1.4</td>
<td>0.869</td>
</tr>
<tr>
<td>Neutrophil count (x10³), mean ± SD</td>
<td>4.3 ± 1.3</td>
<td>4.0 ± 1.0</td>
<td>0.091</td>
</tr>
<tr>
<td>Lymphocyte count (x10³), median (QD)</td>
<td>2.0 (1.7-2.5)</td>
<td>2.3 (1.9-2.7)</td>
<td>0.688</td>
</tr>
<tr>
<td>Monocyte count, median (QD)</td>
<td>380.0 (310.0-460.0)</td>
<td>332.0 (232.0-449.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>ALT (U/L), median (QD)</td>
<td>20.0 (16.0-28.0)</td>
<td>22.0 (17.0-29.0)</td>
<td>0.152</td>
</tr>
<tr>
<td>AST (U/L), median (QD)</td>
<td>20.0 (16.0-24.0)</td>
<td>20.0 (17.0-24.0)</td>
<td>0.246</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl), median (QD)</td>
<td>183.0 (159.0-204.0)</td>
<td>179.0 (152.0-214.8)</td>
<td>0.850</td>
</tr>
<tr>
<td>Triglyceride (mg/dl), median (QD)</td>
<td>105.0 (78.0-150.0)</td>
<td>105.0 (74.0-147.5)</td>
<td>0.981</td>
</tr>
<tr>
<td>LDL (mg/dl), median (QD)</td>
<td>109.0 (94.0-129.0)</td>
<td>113.0 (84.3-140.0)</td>
<td>0.494</td>
</tr>
<tr>
<td>HDL (mg/dl), median (QD)</td>
<td>45.0 (36.0-55.0)</td>
<td>49.0 (43.0-57.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>CRP (mg/L), median (QD)</td>
<td>0.6 (0.3-0.9)</td>
<td>0.5 (0.3-0.8)</td>
<td>0.389</td>
</tr>
<tr>
<td>MHR</td>
<td>9.5 (6.1-12.1)</td>
<td>6.73 (4.7-9.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD or median (QD) or frequency (%).

IBS: Irritable bowel syndrome; BUN: Blood Urea Nitrogen, WBC: white blood cells, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, CRP: C-reactive protein, MHR: monocyte to high-density lipoprotein cholesterol ratio.

Table II: Univariate and multiple logistic regression analysis showing independent predictors in IBS patients.

<table>
<thead>
<tr>
<th></th>
<th>Univariate 95% CI</th>
<th>Multiple 95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>0.003 0.986 1.021</td>
<td>0.724</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.793 0.477 1.319</td>
<td>0.372</td>
<td></td>
</tr>
<tr>
<td>Monocyte</td>
<td>1.002 1.000 1.003</td>
<td>0.033 0.994 0.989</td>
<td>1.000</td>
</tr>
<tr>
<td>HDL</td>
<td>0.975 0.957 0.994</td>
<td>0.010 1.030 0.985</td>
<td>1.076</td>
</tr>
<tr>
<td>MHR</td>
<td>1.115 1.046 1.190</td>
<td>0.001 1.406 1.073</td>
<td>1.843</td>
</tr>
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</table>

HDL: high-density lipoprotein cholesterol, MHR: monocyte to high-density lipoprotein cholesterol ratio.

Figure 1. Receiver operating characteristic (ROC) curve for monocyte to high-density lipoprotein cholesterol ratio as a predictor of IBS.

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DISCUSSION

Accumulating evidence from the literature underscores the involvement of inflammation in the pathophysiology of irritable bowel syndrome (IBS) (5-10). Recently, the Monocyte-to-HDL Ratio (MHR) has emerged as a promising and straightforward marker of inflammation (17, 21). This study was undertaken with the primary objective of elucidating the potential role of MHR in patients diagnosed with IBS.

The key findings of this investigation revealed significantly elevated monocyte counts and reduced HDL cholesterol levels among IBS patients in comparison to the control group. Consequently, the calculated Monocyte-to-HDL Ratios (MHRs) were notably higher in IBS patients. This disparity in MHR between the study and control groups was statistically significant. Furthermore, MHR demonstrated its utility as an independent predictor for IBS, exhibiting a sensitivity of 62.6% and specificity of 63.0% when the cut-off value was set at 7.6. It is worth noting, however, that despite the established independent predictive value of MHR for IBS, the association between MHR and IBS was not found to be exceedingly robust in our study.

The higher MHR levels observed in IBS patients as compared to the control group strongly suggest the potential involvement of inflammation in the pathogenesis of IBS. This intriguing data leads us to hypothesize that therapeutic interventions targeting inflammatory pathways may hold promise for the treatment of IBS. While traditional anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, acetylsalicylic acid, and narcotic analgesics have proven ineffective in IBS management (22), we posit that a deeper understanding of IBS pathophysiology may open new avenues for intervention. This could include targeting well-established inflammatory molecules such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 and potentially addressing monocyte production pathways.

The role of inflammation in IBS has gained support from various studies in the literature. For instance, investigations by Barbara et al. revealed heightened mast cell activity in colonoscopic biopsy specimens of IBS patients (16). Additionally, Liebregts et al. demonstrated elevated levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 in IBS patients compared to controls (21). Furthermore, Güven et al. observed a significantly elevated systemic immune-inflammation index in IBS patients compared to healthy controls (23). Collectively, these studies highlight the role of inflammation in individuals with IBS.

MHR, a novel inflammation marker, has garnered attention across a spectrum of inflammatory disorders. Jiang et al. (24) conducted a large cohort analysis and found a strong correlation between MHR and all-cause and cardiovascular mortality in the general population, even in the presence of established risk factors. In a separate study, MHR was correlated with post-stroke depression at the three-month mark in 411 post-stroke patients (25). Gembillo et al. demonstrated a significant association between MHR and resistant hypertension in patients with chronic renal disease (26).

Moreover, Yalçın et al. found that MHR was a cost-effective and effective marker for assessing ulcerative colitis activity in a study involving 144 ulcerative colitis patients (17). Chen et al. identified the significance of MHR in detecting carotid atherosclerosis in type 2 diabetes mellitus patients (19). Another study by Efe et al. (20) examined MHR as a predictor of inflammation and oxidative stress in acute pulmonary embolism patients and its correlation with mortality. This expanding body of literature exploring the relationship between MHR and inflammatory disorders is continually growing, with some conditions, like fibromyalgia or depression, only recently being linked to inflammation (25, 28) and other associated diseases, including inflammatory bowel diseases, cardiovascular diseases, and pulmonary arterial hypertension, which are well-recognized as inflammatory (17, 19, 27). In the presented study, patients with IBS had significantly higher monocyte counts and lower HDL levels. Thus, higher MHR in IBS patients than in healthy controls suggests the role of inflammation. Moreover, considering the multivariate analyses in the presented study, MHR was identified as an independent predictor for the IBS diagnosis.

This study represents the first exploration of the correlation between MHR and IBS. Nevertheless, it is essential to acknowledge the limitations of our investigation. The retrospective design, small study cohort, and single-center setting are the main limitations. Additionally, subgroup analyses within the IBS category were not feasible in this study. Further research, preferably with a larger and more diverse patient population, is warranted to elucidate the potential clinical utility of MHR in IBS and to better understand the intricate interplay between inflammation and this complex gastrointestinal disorder.

CONCLUSION

This study provides insights into the possible role of inflammation in IBS by investigating the Monocyte-to-HDL Ratio (MHR) as an inflammatory marker. Our findings reveal significantly higher MHR values in IBS patients compared to the control group, suggesting the involvement of inflammation in IBS pathogenesis. While MHR proved to be an independent predictor for IBS diagnosis, the association between MHR and IBS, while statistically significant, was moderate in strength. These results imply the potential for therapies targeting inflammatory pathways in IBS management, supplementing traditional approaches. Our study aligns with existing research indicating inflammation's role in IBS, supported by evidence of increased mast cell activity, elevated proinflammatory cytokines, and a higher systemic immune-inflammation index in IBS patients. In summary, this research highlights the potential significance of MHR as an inflammatory marker in IBS, offering insights into the interplay between inflammation and IBS pathophysiology, with potential implications for improved diagnosis and treatment strategies.

Acknowledgements: None

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Author Contributions: ÇE, İEG, BB, ZMYK; contributed to the conception of the work, execution of the study, revision of the draft, ÇE; approval of the final manuscript version, and concur with all aspects of the work. All authors have reviewed the manuscript, and affirm that they fulfill the ICMJE criteria for authorship.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study.

REFERENCES